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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/510,562	02/22/2000	Gerard Housey	395/35	3061

26646 7590 01/11/2005

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EXAMINER	
GUZO, DAVID	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/510,562	HOUSEY, GERARD	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33,34,36,37,43-50,59-65,71-78 and 87-120* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33,34,36,37,43-50,59-65,71-78 and 87-120* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-34, 36-37, 43-50, 59-65, 71-78, 87-120 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is necessitated by applicant's amendment.

Applicants have amended claims 33, 43, 59, 63, 71 to recite the limitation that the first mammalian cell line which produces the target enzyme (POI) and exhibits a phenotypic response to the enzyme maintains the level of the enzyme **activity** in the cell such that the cell is capable of exhibiting the phenotypic response following removal of the direct inhibitor or activator of the enzyme (this limitation is also recited in new claims 90-120).

The specification does not provide support for the limitation of maintaining the level of target enzyme (POI) **activity** in the cell while in the presence of the potential direct inhibitor or activator such that the cell is capable of exhibiting the phenotypic response following removal of the direct inhibitor or activator of the enzyme. This limitation appears to require that the target enzyme (POI) be enzymatically active in the cell in the presence of the inhibitor or activator. Since the method is dependent upon

observation of a phenotypic response to the enzyme and an observation of whether the chemical agent to be tested exerts an effect on the responsive change in said phenotype, it is unclear how the practitioner of the claimed method could determine whether there is any phenotypic change in the cell in response to the inhibitor if the enzyme is enzymatically active when bound to the inhibitor and presumably still able to exert its effect on the phenotype of the cell. The instant specification does not require that the POI be **enzymatically active** when bound to an inhibitor. This is a NEW MATTER rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33-34, 36-37, 43-50, 59-65, 71-78, 87-120 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is maintained for reasons of record in the previous Office Action (mailed 4/20/04) and for reasons outlined below. It is noted that the examiner inadvertently cited the written description section of 35 USC 112, 1st as the basis for the rejection instead of the enablement requirement of 35 USC 112, 1st paragraph.

However, the rejection was clearly an enablement rejection that included a complete *Wands* factor analysis. The examiner regrets any confusion this may have caused.

Applicant traverses this rejection by asserting that the teachings of the Hsiao et al. reference cited by the examiner are significantly different from applicant's invention. Applicant asserts that Hsiao et al. did not identify a responsive change in a phenotypic characteristic because no correlation was made between $p21^{ras}$ function and $p21^{ras}$ levels in the cells. Applicant asserts that Hsiao et al. provides no basis for disputing the predictability of Applicant's claimed invention, because the work described by Hsiao is significantly different from the instant invention. Applicant asserts that Hsiao's method does not identify a "graded cellular response" or any other responsive change in a phenotypic characteristic and does not identify a POI or an activator or inhibitor of a selected POI.

Applicant also asserts that the significance of applicant's invention is that it provides test cells having phenotypic responses which are particularly sensitive to substances that directly interact with and inhibit or activate an over-expressed enzyme (POI) that evokes the presence of the phenotypic response and thereby enables the identification of a substance that directly interacts with and inhibits or activates the POI. Applicant asserts that a working example is provided in the specification and that applicant has previously cited post-filing references that demonstrate the advantages of relying on cellular function of a POI in cell-based assays to identify compounds that directly bind to a POI.

Applicant's arguments filed 10/25/04 have been fully considered but they are not persuasive. Applicant's critique of Hsiao's work is not really on point here because it appears that applicant's arguments are directed to showing that Hsiao et al.'s work is patentably distinct from that of applicant. The examiner was not using Hsiao et al.'s work as a prior art reference in a 35 USC 103(a) or 102 context but only to indicate the unpredictability of attempting to identify inhibitors of a enzyme based upon the claimed method. Applicant specifically claims the enzyme recited by Hsiao et al. (c-Ha-ras, also known as $p21^{ras}$) as a specific target enzyme whose production in a cell evokes a responsive change (graded cellular response) in a phenotypic characteristic of the cell other than the level of enzyme in the cell (see Claims 87, 117). Hsiao et al. makes it clear that if chemical agents such as TPA or teleocidin were tested against cells expressing the $p21^{ras}$, the skilled artisan would observe a greater phenotypic effect on the test cell line (expressing the $p21^{ras}$ gene product) compared with the control cell line. This would not be correct because TPA or teleocidin does not directly interact with $p21^{ras}$ but instead may function by interacting with protein kinase C receptors or other cellular receptors which in turn interact with the $p21^{ras}$ oncogene product. Indeed, it is also noted that transformed phenotypes induced by $p21^{ras}$ are influenced by c-*fos* expression. It appears that expression of $p21^{ras}$ induces expression of c-*fos* and that the levels of c-*fos* in cells influence, in a titratable fashion, the transformed phenotype in cells. Ledwith et al. (Mol. Cell. Biol., 1990, Vol. 10, No. 4, pp. 1545-1555) shows that cells transformed with $p21^{ras}$ and exhibiting a transformed phenotype resulting from $p21^{ras}$ expression exhibited a graded cellular response (with regard to the transformed

phenotype) to increasing or decreasing levels of c-*fos* (See Fig. 4 in Ledwith et al.). In this case, if the skilled artisan used applicant's method to attempt to identify an inhibitor of $p21^{ras}$ and the test compound actually directly bound to and inhibited c-*fos*, the skilled artisan would erroneously identify the compound as an inhibitor of $p21^{ras}$. It would subsequently require further experimentation (direct binding studies, etc.) in order to identify the true target protein as c-*fos* rather than $p21^{ras}$. Since many eucaryotic enzymes are involved in complex signal transduction pathways in cells, it must be considered that attempting to identify direct inhibitors or activators of any given enzyme by the claimed method would be unpredictable without further experimentation to actually identify whether the test compound actually directly binds to the putative target POI.

With regard to the working example provided in the specification, applicant asserts that said working example identified tamoxifen, which applicant asserts was "...previously known only as an anti-estrogen, to be a PKC inhibitor in a cellular system." (Remarks, p. 19). This is not strictly correct because tamoxifen was previously known to be a PKC inhibitor *in vitro* (See for example, O'Brian et al., 1985, Cancer Research, Vol. 45, pp. 2462-2465, cited by applicant) and applicant's method merely confirmed that a known inhibitor of PKC (tamoxifen) was still an inhibitor in a cellular system. Also, the method as now claimed recites that the level of enzyme activity (in this case PKC activity) in the cell is maintained in the presence of the inhibitor; if this is the case, it is unclear how the skilled artisan would ascertain whether the inhibitor is actually inhibiting the enzyme (see below).

With regard to applicant's arguments concerning the specification providing sufficient guidance for the skilled artisan to practice the claimed invention, the level of skill of the skilled artisan, the nature of the invention, etc., the examiner has previously addressed these arguments in previous Office Actions (See, for example, the Office Action mailed 11/19/02).

In addition, the instantly presented new and amended claims recite that the level of the **enzyme (POI) activity** in the cell is maintained such that the cell is capable of exhibiting the phenotypic response after removal of the inhibitor or activator. If it is assumed that the biological activity of the enzyme is responsible for the phenotypic response in the cell, it is unclear how the skilled artisan could ascertain whether a test compound is a direct inhibitor of said enzyme when the level of enzyme activity is maintained in the cell in the presence of the inhibitor. If the level of enzyme activity is maintained in the presence of a direct (or specific) inhibitor of said enzyme, then the phenotype of the cell should not change in the presence said inhibitor and the skilled artisan would not be able to ascertain whether the test compound exerts a greater effect on the responsive change in phenotype of the first cell relative to the second (control) cell line.

New claims 90-120 recite a method for determining whether a chemical agent specifically inhibits or activates a particular enzyme (POI) in a cell. It must be considered that the outstanding issues relating to enablement and written description are also applicable to these claims. Whether the claims recite a method for determining whether a chemical compound directly or specifically (to the exclusion of other targets)

inhibits a POI, the claimed methods (and specification) do not, for reasons of record, provide a disclosure sufficient to enable and describe the claimed invention.

Claims 33-34, 36-37, 43-50, 59-65, 71-78, 87-120 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is maintained for reasons of record in the previous Office Actions and for reasons outlined below.

Applicant traverses this rejection by reiterating the arguments presented in the traverse of the above 35 USC 112, 1st paragraph, enablement, rejection.

Applicant's arguments filed 10/25/04 have been fully considered but they are not persuasive. For the reasons cited in the above response to applicant's arguments traversing the 112, 1st paragraph, enablement, rejection and for reasons of record, the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 33-34, 36-37, 43-50, 59-65, 71-78, 87-120 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant amended claims 33, 43, 59, 63, 71 to recite the limitation that the first mammalian cell line which produces the target enzyme (POI) and exhibits a phenotypic response to the enzyme **maintains the level of the enzyme activity in the cell** such that the cell is capable of exhibiting the phenotypic response following removal of a direct inhibitor or activator of the enzyme (this limitation is also recited in new claims 90-120). It is unclear what level of enzyme activity is being recited here. It is unclear how a enzyme can maintain its activity when exposed to a direct inhibitor of the enzyme.

Applicant recites in new claims 90-120, a method of determining whether a chemical agent specifically inhibits or activates a particular enzyme in a cell wherein the level of enzyme activity in the cell is maintained such that the cell is capable of exhibiting the phenotypic response following removal of a **direct inhibitor or activator of the enzyme.** It is unclear if the direct inhibitor or activator of the enzyme is the same chemical agent which **specifically inhibits or activates said enzyme** recited in the preamble of the claims or represents another direct activator or inhibitor of the target enzyme.

Any rejections not repeated in this Office Action are withdrawn.

No Claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D., can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DAVID GUZO
PRIMARY EXAMINER

David Guzo
January 6, 2005